CHAPTER 14
Cushing Syndrome

KEY TEACHING POINTS

- The most common cause of Cushing syndrome is exogenous administration of corticosteroid hormones. Endogenous causes are Cushing disease (excess ACTH production from a pituitary tumor), ectopic production of ACTH, and adrenal tumors.
- In patients with suspected disease, the following findings increase the probability of Cushing syndrome: thin skin, ecchymoses, truncal obesity, and osteoporosis.
- In patients with suspected disease, the following findings decrease the probability of Cushing syndrome: generalized obesity, normal skin thickness, and absence of moon facies.
- In patients with ACTH-dependent Cushing syndrome, the presence of significant weight loss or rapid onset of symptoms increases the probability of ectopic ACTH syndrome.
- Pseudo-Cushing syndrome refers to disorders that mimic Cushing syndrome, such as those present in patients with chronic alcoholism or human immunodeficiency virus (HIV)–infected patients taking antiretroviral agents.

I. INTRODUCTION

Cushing syndrome refers to those clinical findings induced by excess circulating glucocorticoids, such as hypertension, central obesity, weakness, hirsutism (in women), depression, skin striae, and bruises. The most common cause is exogenous administration of corticosteroid hormones.[1] Endogenous Cushing syndrome results from pituitary tumors producing the adrenocorticotropic hormone (ACTH; i.e., Cushing disease, 70% of all endogenous cases), ectopic production of ACTH (usually by small cell carcinoma of the lung or carcinoid tumors of the lung or mediastinum, 10% of cases), adrenal adenomas (10% of cases), or adrenal carcinoma (5% of cases).[1] Cushing disease and the ectopic ACTH syndrome are referred to as **ACTH-dependent disease**, because the elevated cortisol levels are accompanied by inappropriately high ACTH levels. Adrenal tumors are indicative of **ACTH-independent disease**.

The bedside findings of Cushing syndrome were originally described by Harvey Cushing in 1932.[2] Corticosteroid hormones were first used as therapeutic agents to treat patients with rheumatoid arthritis in 1949; within 2 years, clear descriptions of exogenous Cushing syndrome appeared.[3]

II. THE FINDINGS AND THEIR PATHOGENESIS

Table 14.1 presents the physical signs of more than 1000 patients with Cushing syndrome.

TABLE 14.1 Cushing Syndrome—Frequency of Individual Findings*

Physical Finding†	Frequency (%)‡
VITAL SIGNS	
Hypertension	64-88
BODY HABITUS	
Moon facies	67-92
Central obesity	44-97
Buffalo hump	34-75
SKIN FINDINGS	
Thin skin	27
Plethora	28-94
Hirsutism, women	48-81
Ecchymoses	23-75
Red or purple striae	46-68
Acne	21-52
EXTREMITY FINDINGS	
Proximal muscle weakness	39-68
Edema	15-66
OTHER	
Significant depression	12-40

*Information is based on 1056 patients from references 4-11. Each study enrolled >50 patients with disease.
†*Diagnostic standard*: For *Cushing syndrome,* elevated daily cortisol or corticosteroid metabolites, or both, with loss of circadian rhythm and with abnormal dexamethasone suppression tests.
‡Results are overall mean frequency or, if statistically heterogeneous, the range of values.

A. BODY HABITUS

Patients with Cushing syndrome develop **central obesity** (also known as **truncal obesity** or **centripedal obesity**), a term describing accumulation of fat centrally on the neck, chest, and abdomen, which contrasts conspicuously with the muscle atrophy affecting the extremities. There are three definitions of central obesity: (1) Obesity sparing the extremities (a subjective definition and also the most common one).[4,12] (2) The **central obesity index**, a complicated ratio of the sum of 3 truncal circumferences (neck, chest, and abdomen) divided by the sum of 6 limb circumferences (bilateral arms, thighs, and lower legs). Values higher than 1 are abnormal.[13] (3) Obesity as defined by an abnormal waist-to-hip circumference ratio (i.e., >1 in men and >0.85 in women; see Chapter 13).[14] The abnormal waist-to-hip circumference is not recommended because there are many false positives (i.e. for Cushing syndrome).

Other characteristic features of the Cushing body habitus are accumulation of fat in the bitemporal region (**moon facies**),[15] between the scapulae and behind the neck (**buffalo hump**), in the supraclavicular region (producing a "collar" around the base of the neck),[14] and in front of the sternum (**dewlap**, named after its resemblance to the hanging fold of skin at the base of the bovine neck; Fig.14.1).[16] Many experts state that the buffalo hump is not specific to Cushing syndrome but accompanies weight gain from any cause;[17,18] this hypothesis has not been formally tested. Morbid obesity is rare in Cushing syndrome.[19]

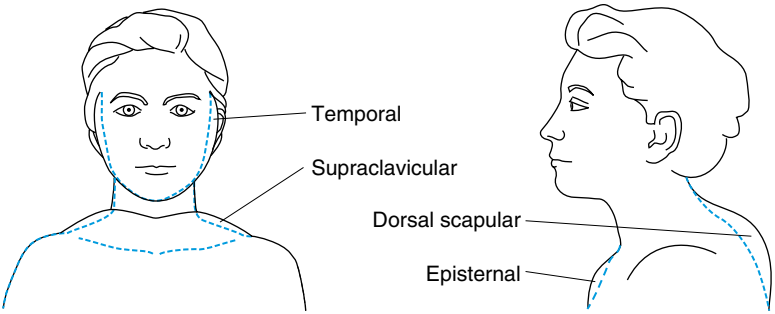


FIG. 14.1 DISTRIBUTION OF ADIPOSE TISSUE IN CUSHING SYNDROME. Rounding of cheeks and prominent bitemporal fat produces the characteristic moon facies. Fat also may accumulate bilaterally above the clavicles (supraclavicular collar), in front of the sternum (episternal area, or dewlap), and over the back of the neck (dorsal cervical fat pad, or buffalo hump). In these drawings, the dotted line depicts normal contours of patients without Cushing syndrome.

The truncal obesity of Cushing syndrome reflects increased intra-abdominal visceral fat, not subcutaneous fat,[20] probably from glucocorticoid-induced reduction in lipolytic activity and activation of lipoprotein lipase, which allows tissues to accumulate triglyceride.

B. HYPERTENSION

Hypertension affects three out of four patients with Cushing syndrome. Proposed mechanisms are suppressed vasodepressor systems (prostaglandins, kallikrein-kinin), exaggerated pressor responses to vasoactive substances, and possible activation of the renin-angiotensin system.[21] Most patients do *not* have a positive salt and water balance.[14]

C. SKIN FINDINGS

The characteristic skin findings associated with Cushing syndrome are thin skin, striae, plethora, hirsutism (in women), acne, and ecchymoses.

Significant thinning of the skin probably arises from corticosteroid-induced inhibition of epidermal cell division and dermal collagen synthesis.[14] To measure skin thickness, many experts recommend using calipers (either skinfold calipers or electrocardiograph calipers) on the back of the patient's hand, an area lacking significant subcutaneous fat and thus representing just epidermis and dermis.[22,23] In women of reproductive age, this skinfold should be thicker than 1.8 mm.[22] Precise cutoffs have not been established for men, whose skin is normally thicker than women's, or for elderly patients, whose skin is normally thinner than younger patients.[23]

The striae in patients presenting with Cushing syndrome are wide (>1 cm) and colored deep red or purple, in contrast to the thinner, paler pink or white striae that occur normally during rapid weight gain of any cause.[4,24] Striae are usually found on the lower abdomen but may occur on the buttocks, hips, lower back, upper thighs, and arms. In one of Cushing's original patients, wide striae extended from the lower abdomen to the axillae.[2] Pathologically, striae are dermal scars, with collagen fibers all aligned in the direction of stress, covered by an abnormally thin epidermis.[25] The pathogenesis of striae is not understood, but they may result from rupture of

the weakened connective tissue of the skin, under tension from central obesity, which leaves a thin translucent window to the red and purple colored dermal blood vessels. Striae are more common in younger patients with Cushing syndrome than in older patients.[24,26]

Plethora is an abnormal, diffuse purple or reddish color of the face.[4] Hirsutism and acne occur because of increased adrenal androgens.[14,24] Ecchymoses probably appear because the blood vessels, lacking connective tissue support and protection, are more easily traumatized.

The severity of striae, acne, and hirsutism correlates poorly with cortisol levels, indicating that other factors—temporal, biochemical, or genetic—play a role in these physical signs.[24]

D. PROXIMAL WEAKNESS

Painless proximal weakness of the legs is common and prominent in Cushing syndrome, especially in elderly patients.[26] Because this weakness is a true myopathy, patients lack fasciculation, sensory changes, or reflex abnormalities. Chapter 61 discusses how to assess proximal muscle strength.

E. DEPRESSION

Patients with Cushing syndrome present with crying episodes, insomnia, impaired concentration, difficulty with memory, and suicide attempts.[27,28] The severity of depression correlates with the cortisol level,[27] and unless the depression antedates the endocrine symptoms by years, it usually improves dramatically after treatment.[28]

F. PSEUDO-CUSHING SYNDROME

Several disorders, including chronic alcoholism, depression, and HIV infection, may mimic the physical and biochemical findings of Cushing syndrome and can thus be categorized as pseudo-Cushing syndrome. Patients with chronic alcoholism may develop the physical findings or the biochemical abnormalities associated with Cushing syndrome, or both, most likely due to the overproduction of ACTH by the hypothalamic-pituitary axis, an abnormality that resolves after several weeks of abstinence.[29,30] Depressed patients may have the biochemical abnormalities of Cushing syndrome, but they usually lack the physical findings.[31] Patients with HIV infection, particularly if they are receiving protease inhibitors, may develop some of the physical findings (especially the buffalo hump and truncal obesity) but rarely the biochemical abnormalities.[32-35]

III. CLINICAL SIGNIFICANCE

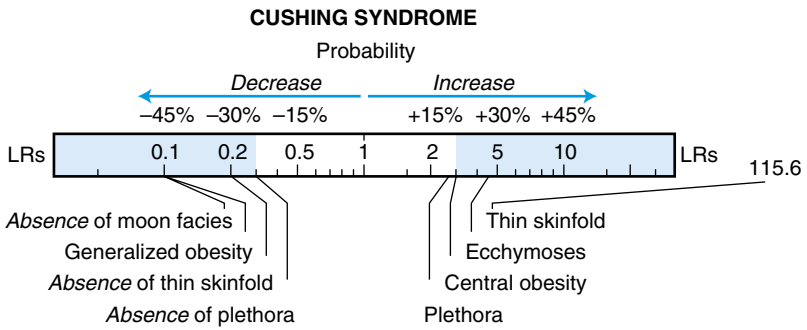
A. DIAGNOSTIC ACCURACY OF FINDINGS

EBM Box 14.1 presents the diagnostic accuracy of individual physical symptoms associated with Cushing syndrome, as applied to 303 patients with suspected disease. The findings that significantly *increase* the probability of Cushing syndrome are thin skinfold (likelihood ratio [LR] = 115.6), ecchymoses (LR = 4.5), central obesity (LR = 3), and plethora (LR = 2.7). (The astronomical LR for thin skinfold thickness [LR = 115.6] derives from young women presenting with hirsutism and menstrual irregularity and thus applies only to similar patients.) The findings that *decrease* the probability of Cushing syndrome are generalized obesity (LR = 0.1),

EBM BOX 14.1
*Cushing Syndrome**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
Vital Signs				
Hypertension[4,12]	25-38	83-94	2.3	0.8
Body Habitus				
Moon facies[12]	98	41	1.6	**0.1**
Central obesity[4,12,13]	72-90	62-97	**3.0**	**0.2**
Generalized obesity[4]	4	38	**0.1**	2.5
BMI >30 kg/m^2 [36]	31	26	0.4	2.6
Skin Findings				
Thin skinfold[22]	78	99	**115.6**	**0.2**
Plethora[4]	83	69	2.7	**0.3**
Hirsutism, in women[4,12,36]	47-76	48-71	NS	NS
Ecchymoses[4,12,36]	38-71	69-94	**4.5**	0.6
Red or blue striae[4,12,36]	41-52	61-78	NS	0.8
Acne[4,36]	25-52	61-76	NS	NS
Extremity Findings				
Muscle weakness[4,12,36]	28-63	69-93	NS	NS
Edema[4,12]	38-57	56-83	1.8	0.7

*Diagnostic standard: for *Cushing syndrome,* elevated daily cortisol or corticosteroid metabolites, or both, with loss of circadian rhythm and abnormal dexamethasone suppression.
†Definition of findings: for *hypertension*, diastolic blood pressure >105 mm Hg; for *central obesity,* central obesity index exceeds 1[13] or there is a subjective appearance of central obesity, sparing the extremities[4,12]; for *thin skinfold,* skinfold thickness on the back of the hand <1.8 mm (women of reproductive age only).[22]
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
Click here to access calculator



absence of moon facies (LR = 0.1), absence of central obesity (LR = 0.2), and normal skinfold thickness (LR = 0.2).

In these same studies, one of the more powerful predictors of Cushing syndrome is osteoporosis (sensitivity of 32% to 63%, specificity of 90% to 97%, positive LR = 8.6, and negative LR = 0.5).[4,12,36] Osteoporosis was identified radiographically in these studies, but it is often apparent at the bedside from vertebral fractures, kyphosis, and loss of height. Presumably, these bedside findings also accurately identify Cushing syndrome.

B. ETIOLOGY OF CUSHING SYNDROME AND BEDSIDE FINDINGS

Patients who take exogenous corticosteroids have the same frequency of central obesity, moon facies, and bruising as patients with endogenous Cushing, but a significantly lower incidence of hypertension, hirsutism, acne, striae, and buffalo humps.[7]

Patients with the ectopic ACTH syndrome from small cell carcinoma are more often male, have Cushing syndrome of rapid onset (over months instead of years), and present with prominent weight loss, myopathy, hyperpigmentation, and edema.[17,31,37] The irregular hepatomegaly of metastatic disease may suggest this diagnosis.[37] In studies of patients with ACTH-dependent Cushing syndrome, two findings increase the probability of ectopic ACTH syndrome: weight loss (positive LR = 20) and symptom duration less than 18 months (positive LR = 15).[9,37]

Hirsutism and acne may occur in any woman with endogenous Cushing syndrome, but the presence of virilization (i.e., male pattern baldness, deep voice, male musculature, clitoromegaly) argues strongly for adrenocortical carcinoma.[38-40]

The references for this chapter can be found on www.expertconsult.com.

REFERENCES

1. Newell-Price J, Bertagna X, Nieman LK. Cushing's syndrome. *Lancet*. 2006;367:1605–1617.
2. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Bull Johns Hopkins Hosp*. 1932;50(3):137–195.
3. Freyberg RH, Traeger CH, Patterson M, Squires W, Adams CH, Stevenson C. Problems of prolonged cortisone treatment for rheumatoid arthritis: further investigation. *J Am Med Assoc*. 1951;147(16):1538–1543.
4. Nugent CA, Warner HR, Dunn JT, Tyler FH. Probability theory in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab*. 1964;24:621–630.
5. Ross EJ, Linch DC. Cushing's syndrome—killing disease: discriminatory value of signs and symptoms aiding early diagnosis. *Lancet*. 1982;2(8299):646–649.
6. Soffer LJ, Iannoccone A, Gabrilove JL. Cushing's syndrome: a study of fifty patients. *Am J Med*. 1961;30:129–146.
7. Liou TC, Lam HC, Ho LT. Cushing's syndrome: analysis of 188 cases. *J Formosan Med Assoc*. 1989;88(9):886–893.
8. Erem C, Algun E, Ozbey N, et al. Clinical laboratory findings and results of therapy in 55 patients with Cushing's syndrome. *J Endocrinol Invest*. 2003;26:65–72.
9. Su DH, Chang YC, Chang TC, Chang CC, Tsai KS, Huang TS. Characteristics of Cushing's syndrome in Taiwanese. *J Formos Med Assoc*. 2003;102(5):292–298.
10. Boscaro M, Arnaldi G. Approach to the patient with possible Cushing's syndrome. *J Clin Endocrinol Metab*. 2009;92:3121–3131.
11. Pecori Giraldi F, Moro M, Cavagnini F. Gender-related differences in the presentation and course of Cushing's disease. *J Clin Endocrinol Metab*. 2003;88(4):1554–1558.
12. Streeten DHP, Stevenson CT, Dalakos TG, Nicholas JJ, Dennick LG, Fellerman H. The diagnosis of hypercortisolism. Biochemical criteria differentiating patients from lean and obese normal subjects and from females on oral contraceptives. *J Clin Endocrinol*. 1969;29:1191–1211.
13. Hiramatsu R, Yoshida K, Sato T. A body measurement to evaluate the pattern of fat distribution in central obesity. A screening and monitoring technique for Cushing's syndrome. *J Am Med Assoc*. 1983;250(23):3174–3178.
14. Yanovski JA, Cutler Jr GB. Glucocorticoid action and the clinical features of Cushing's syndrome. *Endocrinol Metab Clin North Am*. 1994;23(3):487–509.
15. Gottlieb NL. Temporal fat pad sign during corticosteroid treatment. *Arch Intern Med*. 1980;140(11):1507–1508.
16. Lucena GE, Bennett WM, Pierre RV. "Dewlap": a corticosteroid-induced episternal fatty tumor. *N Engl J Med*. 1966;275(15):834–835.
17. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev*. 1998;19(5):647–672.
18. Orth DN. Cushing's syndrome. *N Engl J Med*. 1995;332(12):791–803.
19. Printen KJ, Blommers TJ. Morbid obesity in Cushing's syndrome: a nonentity? *Am J Surg*. 1977;134:579–580.
20. Mayo-Smith W, Hayes CW, Biller BM, Klibanski A, Rosenthal H, Rosenthal DI. Body fat distribution measured with CT: correlations in healthy subjects, patients with anorexia nervosa, and patients with Cushing syndrome. *Radiology*. 1989;170(2):515–518.
21. Saruto T, Suzuki H, Handa M, Igarashi Y, Kondo K, Senba S. Multiple factors contribute to the pathogenesis of hypertension in Cushing's syndrome. *J Clin Endocrinol Metab*. 1986;62(2):275–279.
22. Corenblum B, Kwan T, Gee S, Wong NCW. Bedside assessment of skin-fold thickness: a useful measurement for distinguishing Cushing's disease from other causes of hirsutism and oligomenorrhea. *Arch Intern Med*. 1994;154:777–781.
23. Wright AD, Joplin GF. Skin-fold thickness in normal subjects and in patients with acromegaly and Cushing's syndrome. *Acta Endocrinol (Copenh)*. 1969;60(4):705–711.
24. Stratakis CA, Mastorakos G, Mitsiades NS, Mitsiades CS, Chrousos GP. Skin manifestations of Cushing disease in children and adolescents before and after the resolution of hypercortisolemia. *Pediatr Dermatol*. 1998;15(4):253–258.
25. Arem AJ, Kischer CW. Analysis of striae. *Plast Reconstruct Surg*. 1980;65(1):22–29.
26. Urbanic RC, George JM. Cushing's disease—18 years' experience. *Medicine (Baltimore)*. 1981;60(1):14–24.

27. Starkman MN, Schteingart DE. Neuropsychiatric manifestations of patients with Cushing's syndrome. Relationship to cortisol and adrenocorticotropic hormone levels. *Arch Intern Med*. 1981;141(2):215–219.
28. Jeffcoate WJ, Silverstone JT, Edwards CR, Besser GM. Psychiatric manifestations of Cushing's syndrome: response to lowering of plasma cortisol. *Q J Med*. 1979;48(191):465–472.
29. Kirkman S, Nelson DH. Alcohol-induced pseudo-Cushing's disease: a study of prevalence with review of the literature. *Metabolism*. 1988;37(4):390–394.
30. Veldman RG, Meinders AE. On the mechanism of alcohol-induced pseudo-Cushing's syndrome. *Endocr Rev*. 1996;17(3):262–268.
31. Trainer PJ, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome. *Clin Endocrinol (Oxf)*. 1991;34(4):317–330.
32. Lo JC, Mulligan K, Tai VW, Algren H, Schambelan M. "Buffalo hump" in men with HIV-1 infection. *Lancet*. 1998;351(9106):867–870.
33. Miller KK, Daly PA, Sentochnik D, et al. Pseudo-Cushing's syndrome in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1998;27(1):68–72.
34. Aboulafia DM, Bundow D. Images in clinical medicine. Buffalo hump in a patient with the acquired immunodeficiency syndrome. *N Engl J Med*. 1998;339(18):1297.
35. Tierney EP, Hanke CW. "Bullfrog neck," a unique morphologic trait in HIV lipodystrophy. Case series and review of the literature. *Arch Dermatol*. 2010;146:1279–1282.
36. Pecori Giraldi F, Pivonello R, Ambrogio AG, et al. The dexamethasone-suppressed corticotropin-releasing hormone stimulation test and the desmopressin test to distinguish Cushing's syndrome from pseudo-Cushing's states. *Clin Endocrinol*. 2007;66:251–257.
37. Blunt SB, Sandler LM, Burrin JM, Joplin GF. An evaluation of the distinction of ectopic and pituitary ACTH dependent Cushing's syndrome by clinical features, biochemical tests and radiological findings. *Q J Med*. 1990;77(283):1113–1133.
38. Bertagna C, Orth DN. Clinical and laboratory findings and results of therapy in 58 patients with adrenocortical tumors admitted to a single medical center (1951 to 1978). *Am J Med*. 1981;71(5):855–875.
39. Hutter AM, Kayhoe DE. Adrenal cortical carcinoma: clinical features of 138 patients. *Am J Med*. 1966;41:572–580.
40. Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med*. 1990;322(17):1195–1201.